

Contribution of *Malassezia* spp. to the development of atopic dermatitis

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Summary

The prevalence of atopic dermatitis (AD) has been increasing. Whereas AD symptoms are obvious and easy to recognise, the etiopathogenesis remains not fully elucidated. Recently, the role of microorganisms and their impact on the immunology of AD have been discussed. In this review, we summarise a possible role of *Malassezia* in the development and persistence of eczema in patients with atopic eczema/dermatitis syndrome. A high proportion of AD patients present with a positive reaction to *Malassezia* allergens. Several possible pathogenic mechanisms enable *Malassezia* to trigger the development of AD. *Malassezia* spp. may release more allergens in a less acidic (pH <6), typical for AD, environment. The similarity between fungal thioredoxin and human proteins causes T-cell cross-reactivity. TLR-mediated mechanisms are involved in host response against *Malassezia* spp. An interaction between *Malassezia* spp. and keratinocytes alters the profile of cytokine release, and what is more, yeast cells can survive when absorbed by keratinocytes. Dendritic cells of AD patients induced by *Malassezia* are less susceptible to lysis mediated by NK cells which exerts a pro-inflammatory effect. Despite the evidence that *Malassezia* spp. contribute to the development of AD, the pathogenetic mechanisms and relationship between *Malassezia* and immune defense remain partly unexplained and require further research.

KEYWORDS

atopic dermatitis, immunity, *Malassezia*, mycotic infection

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic multifactorial inflammatory disease of the skin with increasing prevalence over the last decades. Whereas symptoms of AD are obvious and easy to recognise, the etiopathogenesis remains not fully elucidated. The genetic and environmental factors, defects of the epidermal barrier are taken into account, but the role of microorganisms and their impact on the immunology of the disease are increasingly discussed.¹ It has been uncertain over almost two decades if opportunistic *Malassezia* yeast, previously known as *Pityrosporum*, contributes to the development of symptoms and exacerbations of atopic dermatitis.² Currently,

several reports have revealed the presence of specific IgE in the plasma as well as positive patch tests or reactions to *Malassezia* allergens in patients with AD.³ In extracts from *Malassezia*, several components bonding IgE with a molecular mass of 10–100 kDa were identified. The genes coding nine *Malassezia* allergens with a molecular mass of 14–36 kDa were identified and cloned. Recombination techniques allowed production of six of them and their use in diagnostic tests. A high genetic diversity discovered in the *Malassezia* genus that has been seen especially in patients with AD prompted scientists to rebuild the taxonomy and define several new species.² At least seven of currently accepted species has been regularly isolated from human skin; however, their pathogenic properties have

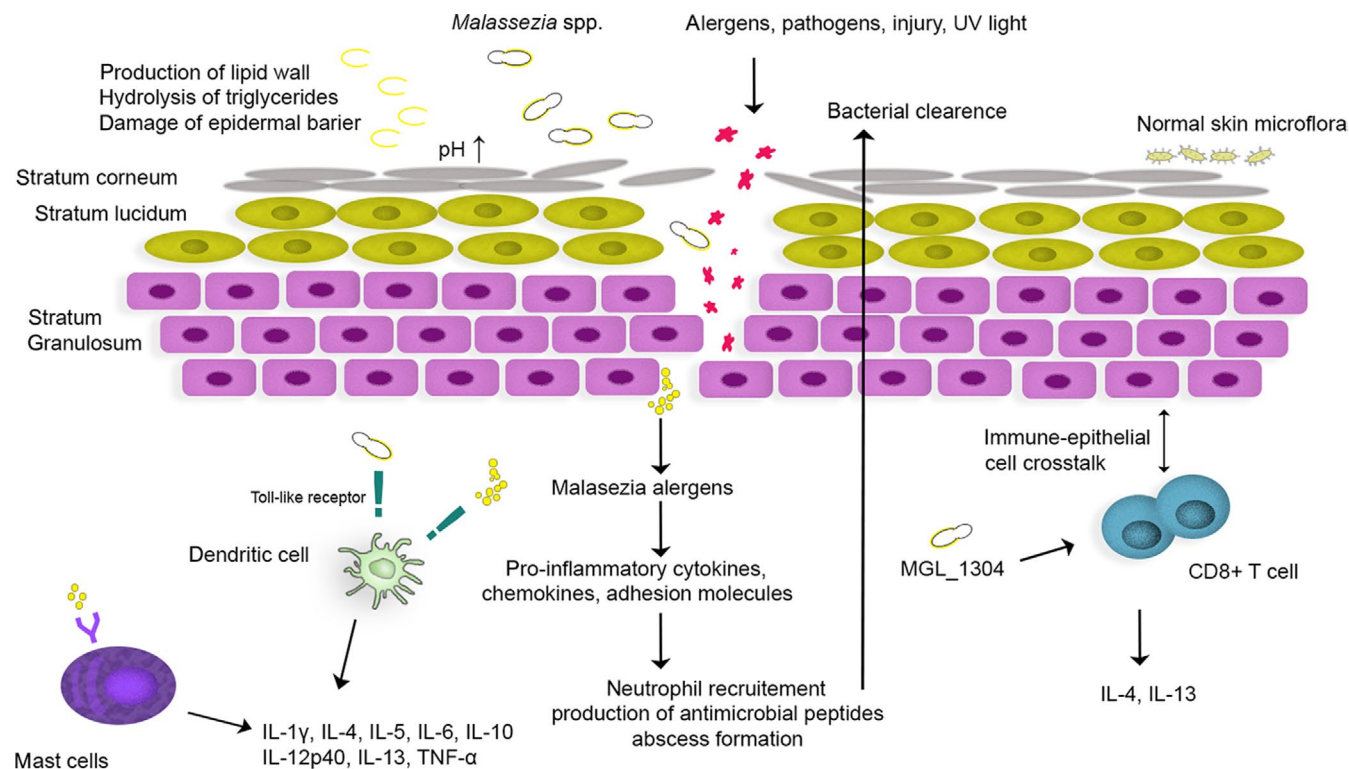


FIGURE 1 Mechanism of *Malassezia* spp. invasion in AD

not been fully understood. Adequate proportions of *Malassezia* spp. allergens in AD have to be elucidated. In the present review, we summarise data on the possible role of *Malassezia* in the development and persistence of eczema in patients with atopic eczema/dermatitis syndrome.⁴

The first reports on the association between AD and *Malassezia* were published by Clemmensen and Hjorth in 1983.⁵ The researchers discovered that treatment with ketoconazole alleviates eczema, particularly in adult patients with head and neck eczema; those patients had a positive skin prick test (SPT) towards *Malassezia*. Several other studies confirmed that the treatment with oral and topical ketoconazole might improve the course of the disease.^{6–8} The intensity of eczema as measured with SCORAD scale was diminished and related to the concentration of serum *Malassezia*-specific IgE and the total serum IgE in patients with AD.^{7,8} The clinical response was greater in patients with positive yeast cultures before the treatment.⁷ Up to date, several reports have been published. They confirm the occurrence of serum specific IgE and positive SPT towards *Malassezia* in patients with AD.^{9–16} Moreover, in patients with AD, positive atopy patch tests (APT) towards *Malassezia* were reported.^{10,11,17} The present paper reviews and discusses *Malassezia* contribution to the development of AD and possible pathogenic mechanism of this fungal infection. The summary of the mechanism involved in *Malassezia* spp. invasion in AD is depicted in Figure 1.

Malassezia yeasts are a part of normal microflora of humans and many warm-blooded animals because the fungi colonise stratum corneum and hair follicles. The yeasts are the most abundant in seborrhoeic areas and skin folds.^{18,19} Colonisation increases during

puberty, when sebaceous glands become more active due to their stimulation mainly by androgen hormones acting through specific receptors.²⁰ Yeast cells divide by unipolar budding. They can be round, oval or cylindrical with a diameter of 1–8 µm. Their cell wall is composed of carbohydrates, proteins and lipids.²¹ Over the years, the yeast taxonomy has been changed and the former name *Pityrosporum* was replaced by currently used *Malassezia*. At present, the *Malassezia* genus is divided into over a dozen species, the majority of which can be isolated from the human skin.²² Except for *Malassezia pachydermatis*, all *Malassezia* species are lipid-dependent and can be cultured only on media supplemented with lipids.²³ *Malassezia* spp. are characterised by a large variety and diverse occurrence.^{24–35} The occurrence of *Malassezia* in humans is summarised in Table 1.

Malassezia spp. are usually harmless but they may cause skin infections under certain conditions or even contribute to generalised infections. In 1846, Eichstedt as first had reported the association between *Malassezia* and pityriasis versicolour while describing yeast-like cells from the stratum corneum of the scalp skin. It has been known that similar to pityriasis, *Malassezia* is a causative factor for folliculitis and plays a significant role in the pathogenesis of seborrhoeic dermatitis.^{36,37}

Taking into account the new taxonomy, associations between *Malassezia* spp. and the diseases they cause seem to be interesting. *M. globosa* and *M. sympodialis* were described as causative factors for pityriasis versicolour. Additionally, *M. globosa*, *M. furfur* and *M. sympodialis* were the most frequent agents isolated from the skin affected with seborrhoeic dermatitis.^{38,39}

TABLE 1 Occurrence of *Malassezia* species in humans (Adapted from: Gaitanis et al.¹)

Species	Distribution of <i>Malassezia</i> species in colonisation and infections				
	Human- healthy skin		Skin disorders		Other infection
	Positive cultures	Detected genetically	Positive cultures	Detected genetically	
<i>Malassezia globosa</i> (1996) ²²	12%-78%-dominate worldwide, except of Canada and Indonesia	44.5%-100%	PV: 14%-97% (Spain, Greece, India) SD: 17.5%-58% (Greece) AD: 16%-28% (Sweden)	PV: 94% SD: 93.5% AD: 16%-100%	
<i>Malassezia sympodialis</i> (1990)	7%-69% (highest in Sweden & Canada)	15%-50%	PV: 5%-63% (Canada) SD: 1%-43% (Sweden) AD: 32%-51% (Canada)	PV: 35% SD: 35.5% AD: 32%-58%	Fungemia Otitis externa
<i>Malassezia restricta</i> (1996) ²²	1%-49% (highest in South Korea)	56%-94%	PV: 0%-9% (Iran) SD: 9%-48% (Greece) AD: 3%-22% (South Korea)	PV: 94% SD: 74% AD: 22%-97%	Keratitis Appendicitis
<i>Malassezia furfur</i> (1889)	4%-23% (Iran)	11%-27%	PV: 1%-41% (Iran) SD: 1%-32% (Iran) AD: 4%-21% (South Korea)	PV: 10% SD: 6.5% AD: 21%-41%	Fungemia Meningitis
<i>Malassezia slooffiae</i> (1996) ²²	1%-7% (50% in Japan)	7%-22%	PV: 1%-16% (Turkey) SD: 0%-15% (Bosnia-Herzegovina) AD: 3%-7% (Sweden)	PV: 8% SD: 39% AD: 3%-51%	
<i>Malassezia obtusa</i> (1996) ²²	0%-15% (Sweden)	10%	PV: 1%-8% (Iran) SD: 43%-Sweden AD: 10%-30% (Canada-Sweden)	PV: 4% SD: 10% AD: 28%	
<i>Malassezia dermatis</i> (2002) ²⁵	2%-4% in South Korea	30%-18.5%	PV: 0.5%-Argentina SD: 3%-8% (South Korea-Canada) AD: 6.5%-South Korea	PV: 24.5% SD: 39% AD: 6%-31%	
<i>Malassezia japonica</i> (2003) ²⁶	ND	4%-10%	SD: 1%-Iran	PV: 4% SD: 13% AD: 58%	
<i>Malassezia yamatoensis</i> (2004) ²⁸	ND	4%-7%	SD	PV: 4% SD: 10% AD: 14%	
<i>Malassezia arunalokei</i> (2016) ³⁰	+		SD: (India)		
<i>Malassezia pachydermatis</i> (1935)	ND		PV: 10.5%-Iran SD: Creotia		Otitis externa in dogs, cats Fungemia
<i>Malassezia nana</i> (2004) ²⁴	Animal (cows, cats)				
<i>Malassezia caprae</i> (2007) ²⁷	Animal (goats)				
<i>Malassezia cuniculi</i> (2011) ²⁹	Animal (rabbits)				
<i>Malassezia equina</i> (2007) ²⁷	Animal (horses)				
<i>Malassezia brasiliensis</i> (2016) ³¹	Animal (parrots)				
<i>Malassezia psittaci</i> (2016) ³¹	Animal (parrots)				

AD, atopic eczema; PV, pityriasis versicolour; SD, seborrhoeic dermatitis.

A lot of papers on AD have been published in the literature but they lead to conflicting conclusions. The most data have been collected on *M. furfur*. Interestingly, studies conducted in Japan highlighted the pathogenic role of *M. globosa* and *M. restricta* because they were isolated from nearly 90% of patients with AD in this region.⁴⁰ Many studies emphasise the role of *M. sympodialis* as a component of the skin microbiota in both healthy individuals and patients with AD.^{41,42} Moreover, recent genomic studies have discovered the presence of *Malassezia* DNA in other areas than skin niches (eg, respiratory and digestive tracts) in humans and animals as well as in the environment.²³ The meta-analysis by Bjerre et al⁴³ revealed that in patients with AD, fungal microbiome showed diminished numbers of *Malassezia* spp. in comparison with healthy individuals, but the presence of *Malassezia dermatis* and other fungal species (eg, *Candida*, *Aspergillus*) was also detected. Moreover, they found an abundance of *Staphylococcus aureus* on the AD skin which correlated positively with the disease severity.

2 | EPIDERMAL BARRIER IN THE SKIN OF PATIENTS WITH AD

Disorders of the epidermal barrier such as impaired structure, renewal and function, in patients with AD seem to play a role in triggering an immune reaction and a nonspecific inflammatory reaction. Increasingly, disorders in the structure of the epidermal barrier are mentioned as one of the factors facilitating bacterial and fungal colonisation. The epidermal barrier prevents excessive loss of water from the epidermis and deeper layers of the skin as well as protects against physical factors such as heat and cold, against penetration of potentially harmful substances and excessive production of physiological flora. The good condition of the epidermal barrier guarantees healthy appearance and proper functioning of the entire skin. Disorders in the skin composition followed by disorders of the skin barrier occur in the course of many diseases. The skin barrier is composed of corneocytes—cells of the stratum corneum, lipids and natural moisturising factor (NMF) produced during the maturation of corneocytes.⁴⁴

In the course of keratinocyte differentiation, components of the extracellular matrix are produced. The stratum corneum is composed mainly of NMF (about 20%), ceramides as a part of the external epidermal matrix (40%-50%) and cholesterol (25%); however, the qualitative and quantitative composition of NMF influences the functioning of the stratum corneum to the greatest degree, despite NMF is not the main component of the epidermis. NMF can absorb and bind water in the protective layer of the epidermis. It consists of free amino acids, mostly pyroglutamic acid, and other substances produced in the course of filaggrin differentiation. It also contains urea and inorganic salts. In the course of terminal differentiation of keratin, a cornified envelope (CE), which protects the epidermal barrier against lytic enzymes, is created. This envelope is composed of filaggrin, loricrin, involucrin, trichohyalin and intermediate keratin filaments. It is worth mentioning that mutations of the gene coding

filaggrin are currently considered one of the most important risk factors for AD and bronchial asthma.⁴⁵

Cholesterol is an important lipid of the stratum corneum. Although cells of the basal layer can absorb this lipid from the circulation, it can be synthesised in the epidermis as well. Alterations to the lipid and fatty acid composition in the skin and ceramide reduction along with the increase in cholesterol in the stratum corneum seem to have a major effect on bacterial colonisation on the skin of AD patients. Studies carried out by Heczko et al revealed that a deficiency in medium-chain-length fatty acids might facilitate *Staphylococcus aureus* colonisation of the epidermis. On the contrary, an increased concentration of capric, caprylic and lauric acid prevents excessive growth of this bacteria.⁴⁶

Another factor that contributes to the increased colonisation of microorganisms on the skin is mechanical damage to the epidermal barrier caused not only by inflammation but also by scratching, environmental factors and contact with detergents. In the skin of atopic patients, elevated pH may amount as high as to 8.⁴⁷

Immune disorders are common in AD. Clinically important are elevated levels of IgE as well as increased levels of specific antibodies against aeroallergens and food allergens accompanied by alterations in the profile of cytokines released by subpopulations of Th1 and Th2 lymphocytes.^{16,48,49} A reduced proportion of the Th1 subpopulation is associated with the suppressed production of interferon (IFN) gamma which may diminish functioning of natural killer (NK) cells and reduce the number of circulating T lymphocytes which in turn results in the increased CD4+/CD8+ ratio. After stimulation by the anti-CD3 antibody (OKT-3) and mitogens, a lymphocyte proliferative response decreases. Similar changes occur in samples collected from skin lesions.^{50,51} Immune disorders in AD also encompass granulocytes and include chemotaxis disorders and reduced capacity for generation of free radicals. The increased number of mast cells producing neurotransmitters is observed. The increased activity of complement seems to be triggered by the anti-IgE complex. The increased level of IgE, which has been already mentioned, increases susceptibility to infections.^{52,53}

3 | PATHOGENETIC MECHANISM OF LESIONS CAUSED BY MALASSEZIA IN PATIENTS WITH AD

The cause of the high prevalence of allergy to *Malassezia* spp. in patients with AD has not been explained, but the role of a combination of skin barrier dysfunction, genetic background and environmental factors are discussed as possible reasons. Several recent studies evaluated a possible association between the intensity of AD and the impact of allergy to *Malassezia* spp. as measured with the level of specific IgE. Glatz et al⁵⁴ examined 132 children and 67 adults with AD. They revealed a significant correlation between the intensity of the disease and *Malassezia* spp.-specific IgE in adults, but not in children. Those results confirmed previous findings from the study on 61 Japanese adults with AD.⁵⁵ The lower prevalence of allergy

to *Malassezia* spp. in children in comparison to adults and the lack of correlation between the severity of AD and *Malassezia* spp.-specific IgE in children may be rooted in poor conditions for *Malassezia* spp. growth in children in comparison to adults. The proportion of lipids in sebum, which is a prerequisite for the skin colonisation in most species of *Malassezia*, is low in children, but increases during puberty and then remains elevated in people up to 50 years of age.⁵⁶ Therefore, allergy to *Malassezia* spp. seems to be the most prevalent in adulthood, while allergy to food and aeroallergens is the most common in childhood. There are several *Malassezia* spp. allergens which may explain IgE-specific response. To date, 13 *Malassezia*-derived allergens from two species (*M. furfur* and *M. sympodialis*) have been identified and listed in the official nomenclature of allergens.⁵⁷ In vitro experiments confirmed that *Malassezia* spp. may release more allergens in a less acidic environment of about pH 6.0 characteristic for the surface of the atopic skin than in a more acidic environment of pH 5.5 characteristic for healthy people. Although allergy to *Malassezia* spp. in adults with AD is common, it is not clear whether the IgE response plays a pathogenic role in the development of the disease or rather it is an indicator of a disease intensity.

The mutual relationship between *Malassezia* spp. and immune system of the skin is the one probable reasons for the development of inflammation in AD patients, for example, *Malassezia* spp. allergen Mala s 13 is fungal thioredoxin which is highly similar to the human protein. CD4⁺ T lymphocytes that react against *Malassezia* spp. yeast thioredoxin are fully cross-reactive to the human enzyme. For this reason, apart from recognition of the fungal enzyme, those T lymphocytes cross-react against the human enzyme triggering an inflammatory process in the skin of patients with AD.⁵⁸ A similar induction of autoreactive T cells was observed for a different *Malassezia* spp. allergen; Mala s 11 is a manganese-dependent superoxide dismutase with a high degree of the sequence identity to the corresponding human enzyme. Similar to Mala s 13, Mala s 11 activates T cells that then react against the human protein and contribute to the development of skin inflammation. The strong correlation between AD severity and allergy to Mala s 11 confirmed the cross-reactivity.⁵⁹ A protein from *M. globosa*, MGL_1304, has been recently identified in the sweat of AD patients. It was determined as a potential allergen that may contribute to skin inflammation in AD. The allergy to this protein also positively correlates with the severity of AD.⁶⁰

Prior studies have indicated that *Malassezia* spp. cells interact with various types of the human skin and immune cells. This induces a pro-inflammatory immune response by the skin and immune cells, which may maintain skin inflammation in AD. It is still unclear how this interaction between *Malassezia* spp. cells and host cells occur, and at least two possible ways of the interaction are hypothesised. First, the impaired skin barrier facilitates the physical encounter between *Malassezia* spp. cells and cells of the epidermis and dermis, such as keratinocytes, Langerhans cells, dermal dendritic cells, natural killer cells and fibroblasts.⁶¹ A second possible mechanism of *Malassezia* spp.–the human cell interaction—might be mediated by immunogenic proteins of *Malassezia* spp.⁶² These proteins that are located

on the external cellular coat of yeasts may induce the increased release of TNF- α , IL-6, IL-8, IL-10 and IL-12p70 by dendritic cells and mast cells.^{63–65} Other proteins such as MGL_1304 induce degranulation of mast cells and the release of IL-4 by basophils.⁶⁶

Some authors suggest that Toll-like receptors (TLRs) mediate the communication between whole *Malassezia* spp. cells or their immunogenic proteins and human cells. TLR play the key role in the innate immune system and are directly engaged in the pathogenesis of many skin diseases as they recognise molecules of many pathogens. It has been discovered that TLR2, in particular, can recognise components of many yeasts including *Malassezia* spp.⁶⁷

Some studies conducted recently confirmed the significance of TLR receptors for the immune response of human cells against *Malassezia* spp. For example, *Malassezia* spp. induce the expression of TLR2 and TLR4 on human keratinocytes, which mediate the increased production of the antimicrobial peptide human beta-defensin 2 and the chemokine CXCL8. Others attribute the pro-inflammatory response of dendritic cells against *Malassezia* spp. to TLR-mediated mechanisms.^{68,69}

Watanabe et al were the first to examine the relationship between *Malassezia* spp. and keratinocytes—the most abundant cells with structural and immune functioning in the epidermis. In their study, *M. furfur*, *M. pachydermatis*, *M. slooffiae* and *M. sympodialis* cells were used. The concentration of IL1 β , IL6, IL8, TNF α and monocyte chemotactic protein 1 (MCP1) was measured in the supernatant of the co-culture of keratinocytes and yeast cells at a ratio of 1:1. Cells were cultured for 24 hours, wherein the concentration of cytokine examined was measured at one-hour intervals. The concentration of MCP1 from all species tested was undetectable or low at every measurement. In the supernatant of *M. furfur* culture, the presence of the remaining cytokines was not detected at all, or their concentration was very low. The highest concentration of cytokines was found in the supernatant from the cultures of *M. pachydermatis*, which can be the possible reason for the greater severity of the inflammatory reaction in the course of *M. pachydermatis* infection in animals in comparison to symptoms that appear in humans.⁷⁰ Another study conducted by Baroni et al in 2001 showed that keratinocytes stimulated by *M. furfur* produced decreased amounts of IL1 α and increased amounts of IL-10 and TGF- β 1, leading to an inhibition of IL-6 and TNF α . *Malassezia* cells were absorbed by keratinocytes, but only a small percentage of them were killed. Researchers postulated that the inhibition of IL-1 α , IL-6 and TNF- α secretion allows *Malassezia* spp. survive inside the host cells without inducing an inflammatory reaction.⁷¹ In 1998, Kesavan et al revealed a suppression of IL-1 β , IL-6 and TNF- α by peripheral blood mononuclear cells (PBMC). The same study showed that the suppression of pro-inflammatory cytokines was IL-10-dependent.⁷² The suppression of keratinocytes by *Malassezia* spp. was confirmed by an in vitro study conducted in 2004. Various species of *Malassezia* induce production of IL-1 β , IL-4, IL-5, IL-13 and IL-18 in dendritic cells of the skin; hence, they can activate an NLRP3 inflammasome. Additionally, mast cells from patients suffering from AD release elevated amounts of IL-6

in response to *M. sympodialis* exposure. This increased excretion of cytokines by human cells suggests that the growth of the yeast population contributes to the development and increased severity of the inflammatory process in patients with AD. Interactions between *Malassezia* spp. and dendritic cells have been the subject of many studies since 2000. The majority of authors have evaluated the impact of *Malassezia* spp. on Langerhans cells of skin lesions in patients with AD. In the study conducted in 2000, Buentke et al⁶¹ showed the ability of CD1a+ dendritic cells isolated from peripheral blood to absorb whole *M. furfur* cells, various fungal components and the recombinant Mala f5 allergen. The study also revealed that immature dendritic cells were significantly more effective in up taking *Malassezia* spp. cells than mature cells via mannose receptor-mediated endocytosis. Endocytosis of fungal antigens induced maturation of dendritic cells resulting in the increased production of TNF- α , IL1- β and IL-18. Further, mature dendritic cells stimulated the proliferation of autologous T lymphocytes. In another study, the same authors evaluated interactions between dendritic cells and *Malassezia* spp. cells. Buentke et al reported that the skin specimens collected from patients with AD had a significantly lower number of NK cells than from those collected from healthy individuals.⁷³ Researchers incubated dendritic cells with *Malassezia* spp. cells for 46 hours and next, they examined a degree of dendritic cell lysis mediated by NK cells. This study revealed that co-incubation of dendritic cells with *Malassezia* spp. cells exerts a protective effect and significantly reduces the susceptibility of dendritic cells to lysis as well as stimulates the production of IL-8, IL-6 and IFN- γ . The authors suggest that mature dendritic cells present *Malassezia* spp. antigens to T cells, thus, resistant to lysis by NK cells, they can contribute to the maintenance of the inflammatory response in lesions of patients with AD. This process can be further intensified by pro-inflammatory cytokines produced by dendritic cells. Gabrielsson et al⁷⁴ revealed that dendritic cells of AD patients respond differently to incubation with *Malassezia* spp. cells than those of healthy individuals. The study showed a 5-fold increase in expression of the following

genes: IL-8, CD-54, CD-83, IL-1R, BTG1 (B-cell translocation gene 1) and MDC (monocyte-derived chemokine) in dendritic cells of AD patients after incubation with *M. sympodialis* in comparison to the gene expression in dendritic cells of healthy controls. This may explain the different role of *Malassezia* spp. in both groups.

Some virulence factor produced by *Malassezia* spp. such as fungal enzymes and metabolites significantly contributes to the development of AD. During the colonisation of healthy skin, yeasts produce low levels of phospholipases and lipases, but in the course of the disease, their expression becomes very high, thus play a role in the damage to the epidermal barrier. Additionally, in the in vivo settings, *Malassezia* produces cell wall melanin and several bioactive indoles, for example, indirubin and indolo [3,2-b] carbazole, interacting with the human AhR (aryl-hydrocarbon receptor), and in this way increases UV damage, apoptosis, cell cycle and carcinogenesis, and can stimulate both adaptive and innate immunity.²³

4 | MYCOLOGICAL EXAMINATION AND SUSCEPTIBILITY TO ANTIFUNGALS

Due to unique metabolic features, the culture of *Malassezia* from clinical samples as well as subsequent species identification are difficult and require the use of special media (eg, Dixon agar) and often advanced technology (rDNA sequencing; MALDI-TOF-MS). The susceptibility tests are currently not recommended routinely; however, a few methods have been described in the literature. Many authors have increasingly reported the isolates resistant to commonly used azoles (fluconazole, ketoconazole). The susceptibility profiles seem to be species-specific; for example, *M. obtusa* and *M. caprae* were found resistant to almost all antimycotics used. It is worth noting that similar to other basidiomycetous yeasts (eg, *Cryptococcus* or *Trichosporon*), the genus *Malassezia* is fully resistant to echinocandins, drugs used in the treatment of candidemia. Amphotericin B and triazoles are recommended in the therapy of fungemia due to *Malassezia*.^{75,76}

TABLE 2 Therapeutic approach to infections caused by *Malassezia* spp. in atopic dermatitis

Standard approach		
Options	Treatment option and skin care	New approach
Allergens and other irritant factors	Atopy patch tests, skin prick tests. Identification and elimination of triggering factors.	
Prevention and protection	Proper skin care: emollients, lipid creams, pH neutral soaps. Reconstruction of the impaired skin barrier and reduction in transepidermal water loss.	Additional ingredients and structure of preparations (eg, polidocanol, urea)
Topical anti-inflammatory agents	Calcineurin inhibitors (tacrolimus, pimecrolimus) target activated T cells and reduce skin rash. Topical steroids should be used in caution due to their side effects. They may reduce bacterial colonisation.	Herbal medicine (eg, green tea extracts which include catechins).
Antifungal therapy	Systemic antifungal therapy: azole antifungal agents: miconazole, ketoconazole, itraconazole. Antifungal and anti-inflammatory properties by inhibiting the production of IL-4 and IL-5 by T lymphocytes.	Photodynamic therapy

5 | THERAPEUTIC IMPLICATIONS

The most effective therapy for patients with AD includes an excellent skin care conducted with the aim to reconstruct the impaired skin barrier, reduce inflammatory response with topical steroids or calcineurin inhibitors, as well as the identification and elimination of triggering factors. The importance of antifungal therapy for AD has been discussed for many years. Azole antifungal agents are the most common class of antifungal drugs prescribed for AD patients.⁷⁷ In the clinical practice, improvement after topical use of ketoconazole in patients with head and neck lesions in the course of AD seems to result from the beneficial effect of the overlap of AD symptoms of seborrhoeic dermatitis on the population of *M. furfur*. However, the placebo-controlled study on head and neck lesions in AD that compared topical miconazole-hydrocortisone cream and ketoconazole shampoo to the use of hydrocortisone alone did not show any difference between those treatment regimens. The impact of topical antifungal agents in comparison to topical steroids or calcineurin inhibitors has not been examined to date, although several randomised, placebo-controlled trials have been conducted to evaluate the benefits of systemic antifungal treatments.⁷⁸

Interestingly, azole antifungal agents such as ketoconazole or itraconazole have anti-inflammatory properties. It has been found that those agents inhibit IL-4 and IL-5 production by T lymphocytes which might reduce the inflammatory process and therefore contribute to the improvement of eczema during antifungal treatment.⁷⁹ Another therapeutic approach for AD, particularly against *Malassezia* spp., might be photodynamic therapy. It has been shown that after *M. furfur* had been cultured with a cationic photosensitiser, the irradiation with a 670-nm diode laser significantly decreased the viability of its culture. However, the relevance of these results in the daily clinical practice still needs to be proved.⁸⁰ Therapeutic options employed in the case of infection with *Malassezia* spp. are presented in Table 2.

According to the PubMed database, more than 300 research articles on the association between AD and *Malassezia* were published in between 1985 and 2018. This number included several extensive reviews,^{1,81-83} analysing multiple aspects of the issue including epidemiology, mycological, immune response and therapy. The number of papers covering *Malassezia* in the title and abstract exceeded 1760 (29.11.2018). The presented study reviewed only a small part of reach literature on the topic, which was subjectively selected, but in the opinion of the authors were most relevant. The consensus is that *Malassezia* spp. play an important role in AD. This yeast may interact with the skin immune system. The impaired skin barrier of atopic individuals and sensitisation against *Malassezia* spp. correlates with the severity of AD. Additionally, the antifungal therapy brings beneficial effects in some patients. The pathogenetic mechanism and mutual interaction between *Malassezia* and AD remain partly unclear and need further investigation.

CONFLICT OF INTEREST

None declared.

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REFERENCES

- Gaitanis G, Magiatis P, Hantschke M, et al. The *Malassezia* genus in skin and systemic diseases. *Clin Microbiol Rev*. 2012;25:106-141.
- Han SH, Cheon HI, Hur MS, et al. Analysis of the skin mycobio-
biome in adult patients with atopic dermatitis. *Exp Dermatol*. 2018;27:366-373.
- Wichmann K, Heratizadeh A, Werfel T. In-vitro diagnostic in atopic dermatitis: options and limitations. *Allergol Select*. 2017;1:150-159.
- Faergemann J. *Pityrosporum* species as a cause of allergy and infection. *Allergy*. 1999;54:413-419.
- Clemmensen O, Hjorth N. Treatment of dermatitis of the head and neck with ketoconazole in patients with type I sensitivity to *Pityrosporum orbiculare*. *Semin Dermatol*. 1983;2:26-29.
- Back O, Scheynius A, Johansson SG. Ketoconazole in atopic dermatitis: therapeutic response is correlated with decrease in serum IgE. *Arch Dermatol Res*. 1995;287:448-451.
- Lintu P, Savolainen J, Kortekangas-Savolainen O, et al. Systemic ketoconazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. *Allergy*. 2001;56:512-517.
- Back O, Bartosik J. Systemic ketoconazole for yeast allergic patients with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2001;15:34-38.
- Nordvall SL, Johansson S. IgE antibodies to *Pityrosporum orbiculare* in children with atopic diseases. *Acta Paediatr Scand*. 1990;79:343-348.
- Kieffer M, Bergbrant IM, Faergemann J, et al. Immune reactions to *Pityrosporum ovale* in adult patients with atopic and seborrheic dermatitis. *J Am Acad Dermatol*. 1990;22:739-742.
- Rokugo M, Tagami H, Usuba Y, et al. Contact sensitivity to *Pityrosporum ovale* in patients with atopic dermatitis. *Arch Dermatol*. 1990;126:627-632.
- Wessels MW, Doekes G, Van Ieperen-Van Kijk AG, et al. IgE antibodies to *Pityrosporum ovale* in atopic dermatitis. *Br J Dermatol*. 1991;125:227-232.
- Scalabrin DM, Bavbek S, Perzanowski MS, et al. Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and nonasthmatic control subjects. *J Allergy Clin Immunol*. 1999;104:1273-1279.
- Kim TY, Jang IG, Park YM, et al. Head and neck dermatitis: the role of *Malassezia furfur*, topical steroid use and environmental factors in its causation. *Clin Exp Dermatol*. 1999;24:226-231.
- Mayser P, Gross A. IgE antibodies to *Malassezia furfur*, *M. sympodialis* and *Pityrosporum orbiculare* in patients with atopic dermatitis, seborrheic eczema or pityriasis versicolor, and identification of respective allergens. *Acta Derm Venereol*. 2000;80:357-361.
- Brodzka P, Panzner P, Pizinger K, et al. IgE-mediated sensitization to *Malassezia* in atopic dermatitis: more common in male patients and in head and neck type. *Dermatitis*. 2014;25:120-126.
- Tengvall LM, Johansson C, Scheynius A, et al. Positive atopy patch test reactions to *Pityrosporum orbiculare* in atopic dermatitis patients. *Clin Exp Allergy*. 2000;30:122-131.
- Faergemann J, Aly R, Maibach HI. Quantitative variations in distribution of *Pityrosporum orbiculare* on clinically normal skin. *Acta Derm Venereol*. 1983;63:346-348.
- Jagielski T, Rup E, Macura AB, et al. [Characteristics of *Malassezia* yeasts. I. Microbiological and immunological aspects]. *Post Mikrobiol*. 2013;52:295-305.
- Faergemann J, Fredriksson T. Age incidence of *Pityrosporum orbiculare* on human skin. *Acta Derm Venereol*. 1980;60:531-533.

21. Mittag H. Fine structural investigation of *Malassezia furfur* II. The envelope of the yeast cells. *Mycoses*. 1995;38:13-21.
22. Gueho E, Midgley G, Guillot J. The genus *Malassezia* with description of four new species. *Antonie Van Leeuwenhoek*. 1996;69:337-355.
23. Velegraki A, Cafarchia C, Gaitanis G, et al. *Malassezia* infections in humans and animals: pathophysiology, detection, and treatment. *PLoS Pathog*. 2015;11:e1004523.
24. Hirai A, Kano R, Makimura K, et al. *Malassezia nana* sp. nov., a novel lipid-dependent yeast species isolated from animals. *Int J Syst Evol Microbiol* 2004;54:623-627.
25. Sugita T, Takashima M, Shinoda T, et al. New yeast species, *Malassezia dermatis*, isolated from patients with atopic dermatitis. *J Clin Microbiol*. 2002;40:1363-1367.
26. Sugita T, Takashima M, Kodama M, et al. Description of a new yeast species, *Malassezia japonica*, and its detection in patients with atopic dermatitis and healthy subjects. *J Clin Microbiol*. 2003;41:4695-4699.
27. Cabanes FJ, Theelen B, Castella G, et al. Two new lipid-dependent *Malassezia* species from domestic animals. *FEMS Yeast Res*. 2007;7:1064-1076.
28. Sugita T, Tajima M, Takashima M, et al. A new yeast, *Malassezia yamatoensis*, isolated from a patient with seborrheic dermatitis, and its distribution in patients and healthy subjects. *Microbiol Immunol*. 2004;48:579-583.
29. Cabanes FJ, Vega S, Castella G. *Malassezia cuniculi* sp. nov., a novel yeast species isolated from rabbit skin. *Med Mycol*. 2011;49:40-48.
30. Honnavar P, Prasad GS, Ghosh A, et al. *Malassezia arunalokei* sp. nov., a novel yeast species isolated from seborrheic dermatitis patients and healthy individuals from India. *J Clin Microbiol*. 2016;54:1826-1834.
31. Cabanes FJ, Coutinho SD, Puig L, et al. New lipid-dependent *Malassezia* species from parrots. *Rev Iberoam Micol*. 2016;33:92-99.
32. Oliveri S, Trovato L, Betta P, et al. *Malassezia furfur* fungaemia in a neonatal patient detected by lysis-centrifugation blood culture method: first case reported in Italy. *Mycoses*. 2011;54:e638-e640.
33. Suzuki T, Hori N, Miyake T, et al. Keratitis caused by a rare fungus, *Malassezia restricta*. *Jpn J Ophthalmol*. 2007;51:292-294.
34. Giusiano G, Mangiaterra M, Saito VG, et al. Etiology of fungaemia and catheter colonisation in Argentinean paediatric patients. *Mycoses*. 2006;49:49-54.
35. Harada K, Saito M, Sugita T, et al. *Malassezia* species and their associated skin diseases. *J Dermatol*. 2015;42:250-257.
36. Eichstedt E. Pilzbildung in der Pityriasis versicolor. *Froriep Neue Notizen Geb Naturkunde Heilkunde*. 1846;39:270-271.
37. Thayikkannu AB, Kindo AJ, Veeraraghavan M. *Malassezia*-can it be ignored? *Indian J Dermatol*. 2015;60:332-339.
38. Crespo Erchiga V, Ojeda Martos A, Vera Casaño A, Crespo Erchiga A, Sanchez Fajardo F. *Malassezia globosa* as the causative agent of Pityriasis versicolor. *Br J Dermatol*. 2000;143:799-803.
39. Nakabayashi A, Sei Y, Guillot J. Identification of *Malassezia* species isolated from patients with seborrheic dermatitis, atopic dermatitis, Pityriasis versicolor and normal subjects. *Med Mycol*. 2000;38:337-341.
40. Sugita T, Suto H, Unno T, et al. Molecular analysis of *Malassezia* microflora on the skin of atopic dermatitis patients and healthy subjects. *J Clin Microbiol*. 2001;39:3486-3490.
41. Jagielski T, Rup E, Ziolkowska A, et al. Distribution of *Malassezia* species on the skin of patients with atopic dermatitis, psoriasis, and healthy volunteers assessed by conventional and molecular identification methods. *BMC Dermatol*. 2014;14:3.
42. Prohic A, Jovovic ST, Kuskunovic-Vlahovljak S, et al. Distribution of *Malassezia* species in patients with different dermatological disorders and healthy individuals. *Acta Dermatovenol Croat*. 2016;24:274-281.
43. Bjerre RD, Bandier J, Skov L, et al. The role of the skin microbiome in atopic dermatitis: a systematic review. *Br J Dermatol*. 2017;177:1272-1278.
44. Jungersted JM, Scheer H, Mempel M, et al. Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema. *Allergy*. 2010;65:911-918.
45. Hon KL, Leung AK. Use of ceramides and related products for childhood-onset eczema. *Recent Pat Inflamm Allergy Drug Discov*. 2013;7:12-19.
46. Heczko PB, Kaspruwicz A, Kucharczyk J. [Carrier state of *Staphylococcus aureus*. Susceptibility to free fatty acids of the representatives of the flora from the human nasal cavity]. *Med Dosw Mikrobiol*. 1971;23:205-210.
47. Proksch E. pH in nature humans skin. *J Dermatol* 2018;45:1044-1052.
48. Mittermann I, Wikberg G, Johansson C, et al. IgE sensitization profiles differ between adult patients with severe and moderate atopic dermatitis. *PLoS One*. 2016;11:e0156077.
49. Jain C, Das S, Ramachandran VG, et al. *Malassezia* yeast and cytokine gene polymorphism in atopic dermatitis. *J Clin Diagn Res*. 2017;11:DC01-DC05.
50. Elliott ST, Hanifin JM. Delayed cutaneous hypersensitivity and lymphocyte transformation: dissociation in atopic dermatitis. *Arch Dermatol*. 1979;115:36-39.
51. Chan S, Henderson WR Jr, Li SH, et al. Prostaglandin E2 control of T cell cytokine production is functionally related to the reduced lymphocyte proliferation in atopic dermatitis. *J Allergy Clin Immunol*. 1996;97:85-94.
52. Agrawal R, Woodfolk JA. Skin barrier defects in atopic dermatitis. *Curr Allergy Asthma Rep*. 2014;14:433.
53. Liu FT, Goodarzi H, Chen HY. IgE, mast cells, and eosinophils in atopic dermatitis. *Clin Rev Allergy Immunol*. 2011;41:298-310.
54. Glatz M, Buchner M, von Bartenwerffer BW, et al. *Malassezia* spp.-specific immunoglobulin E level is a marker for severity of atopic dermatitis in adults. *Acta Derm Venereol*. 2015;95:191-196.
55. Zhang E, Tanaka T, Tajima M, et al. Anti-*Malassezia*-specific IgE antibodies production in Japanese patients with head and neck atopic dermatitis: relationship between the level of specific IgE antibody and the colonization frequency of cutaneous *Malassezia* species and clinical severity. *J Allergy (Cairo)*. 2011;2011:645670.
56. Cotterill JA, Cunliffe WJ, Williamson B, et al. Age and sex variation in skin surface lipid composition and sebum excretion rate. *Br J Dermatol*. 1972;87:333-340.
57. WHO/IUIS. Allergen Nomenclature Sub-Committee. Allergen Nomenclature. <http://www.allergen.org/>. 2018. 20-7-2018. Accessed July 20, 2018.
58. Balaji H, Heratizadeh A, Wichmann K, et al. *Malassezia sympodialis* thioredoxin-specific T cells are highly cross-reactive to human thioredoxin in atopic dermatitis. *J Allergy Clin Immunol*. 2011;128:92-99.
59. Schmid-Grendelmeier P, Fluckiger S, Disch R, et al. IgE-mediated and T cell-mediated autoimmunity against manganese superoxide dismutase in atopic dermatitis. *J Allergy Clin Immunol*. 2005;115:1068-1075.
60. Hiragun M, Hiragun T, Ishii K, et al. Elevated serum IgE against MGL_1304 in patients with atopic dermatitis and cholinergic urticaria. *Allergol Int*. 2014;63:83-93.
61. Buentke E, Scheynius A. Dendritic cells and fungi. *APMIS*. 2003;111:789-796.
62. Sparber F, LeibundGut-Landmann S. Host responses to *Malassezia* spp. in the mammalian skin. *Front Immunol* 2017;8:1614.
63. Gehrmann U, Qazi KR, Johansson C, et al. Nanovesicles from *Malassezia sympodialis* and host exosomes induce cytokine responses—novel mechanisms for host-microbe interactions in atopic eczema. *PLoS One*. 2011;6:e21480.

64. Vilhelmsson M, Johansson C, Jacobsson-Ekman G, et al. The *Malassezia sympodialis* allergen Mala s 11 induces human dendritic cell maturation, in contrast to its human homologue manganese superoxide dismutase. *Int Arch Allergy Immunol*. 2007;143:155-162.
65. Selander C, Engblom C, Nilsson G, et al. TLR2/MyD88-dependent and -independent activation of mast cell IgE responses by the skin commensal yeast *Malassezia sympodialis*. *J Immunol*. 2009;182:4208-4216.
66. Hiragun T, Ishii K, Hiragun M, et al. Fungal protein MGL_1304 in sweat is an allergen for atopic dermatitis patients. *J Allergy Clin Immunol*. 2013;132:608-615.
67. Baker BS. The role of microorganisms in atopic dermatitis. *Clin Exp Immunol*. 2006;144:1-9.
68. Brasch J, Morig A, Neumann B, et al. Expression of antimicrobial peptides and toll-like receptors is increased in Tinea and Pityriasis versicolor. *Mycoses*. 2014;57:147-152.
69. Baroni A, Orlando M, Donnarumma G, et al. Toll-like receptor 2 (TLR2) mediates intracellular signalling in human keratinocytes in response to *Malassezia furfur*. *Arch Dermatol Res*. 2006;297:280-288.
70. Watanabe S, Koike A, Kano R, et al. In vitro susceptibility of *Malassezia pachydermatis* isolates from canine skin with atopic dermatitis to ketoconazole and itraconazole in East Asia. *J Vet Med Sci*. 2014;76:579-581.
71. Baroni A, Perfetto B, Paoletti I, et al. *Malassezia furfur* invasiveness in a keratinocyte cell line (HaCat): effects on cytoskeleton and on adhesion molecule and cytokine expression. *Arch Dermatol Res*. 2001;293:414-419.
72. Kesavan S. Immunomodulation by *Malassezia* species. 1998. University of Leeds. 21-7-2018.
73. Buentke E, Zargari A, Heffler LC, et al. Uptake of the yeast *Malassezia furfur* and its allergenic components by human immature CD1a+ dendritic cells. *Clin Exp Allergy*. 2000;30:1759-1770.
74. Gabrielsson S, Buentke E, Lieden A, et al. *Malassezia sympodialis* stimulation differently affects gene expression in dendritic cells from atopic dermatitis patients and healthy individuals. *Acta Derm Venereol*. 2004;84:339-345.
75. Arendrup MC, Boekhout T, Akova M, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect*. 2014;20(Suppl 3):76-98.
76. Leong C, Buttafuoco A, Glatz M, et al. Antifungal susceptibility testing of *Malassezia* spp. with an optimized colorimetric broth microdilution method. *J Clin Microbiol*. 2017;55:1883-1893.
77. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy Asthma and Immunology/PRACTALL Consensus Report. *Allergy*. 2006;61:969-987.
78. Broberg A, Faergemann J. Topical antimycotic treatment of atopic dermatitis in the head/neck area. A double-blind randomised study. *Acta Derm Venereol*. 1995;75:46-49.
79. Kanda N, Enomoto U, Watanabe S. Anti-mycotics suppress interleukin-4 and interleukin-5 production in anti-CD3 plus anti-CD28-stimulated T cells from patients with atopic dermatitis. *J Invest Dermatol*. 2001;117:1635-1646.
80. Takahashi H, Nakajima S, Sakata I, et al. Antifungal effect of TONS504-photodynamic therapy on *Malassezia furfur*. *J Dermatol*. 2014;41:895-897.
81. Darabi K, Hostetler SG, Bechtel MA, et al. The role of *Malassezia* in atopic dermatitis affecting the head and neck of adults. *J Am Acad Dermatol*. 2009;60:125-136.
82. Glatz M, Bosshard P, Schmid-Grendelmeier P. The role of fungi in atopic dermatitis. *Immunol Allergy Clin North Am*. 2017;37:63-74.
83. Glatz M, Bosshard PP, Hoetzenecker W, et al. The role of *Malassezia* spp. in atopic dermatitis. *J Clin Med*. 2015;4:1217-1228.

How to cite this article: Nowicka D, Nawrot U. Contribution of *Malassezia* spp. to the development of atopic dermatitis. *Mycoses*. 2019;62:588-596. <https://doi.org/10.1111/myc.12913>